UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,373	08/03/2007	Edward M. Medof	200512.00047	9970

21324 7590 06/04/2010

HAHN LOESER & PARKS, LLP
One GOJO Plaza
Suite 300
AKRON, OH 44311-1076

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
06/04/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@hahnlaw.com
akron-docket@hotmail.com

Office Action Summary	Application No.	Applicant(s)	
	10/597,373	MEDOF ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *8-11 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 12 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 April 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/7/06; 11/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-18 are pending.

2. Applicant's election with traverse of Group I, Claims 1-7, 12 and 14-18 drawn to a protein comprising: a first functional unit of a first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; a first spacer sequence of at least about 200 amino acids encoding a polypeptide that does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, a polypeptide providing a functional unit of a second complement regulatory protein, a protein having at least 95 percent sequence homology to a protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ IDNO: 19 and SEQ ID NO: 23 and a method of regulating complement activity comprising administering an effective amount of said protein, filed March 3, 2010, is acknowledged.

The traversal is on the basis that Inventions I and II share a common special technical feature. Specifically, the Applicants maintain that the claims of Invention I are drawn to a protein, while the claims of Invention II are drawn to a polynucleotide encoding such a protein. The special technical feature that is common to both alleged Inventions is the claimed protein. Therefore, the alleged inventions form a single general inventive concept under PCT Rule 13.1. Reconsideration and withdrawal of the requirement to elect one invention to be examined is respectfully requested.

Applicants' traversal has been fully considered but is not deemed persuasive. As stated in the restriction requirement mailed February 3, 2010, the inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under unity of invention practice as it applies to cases filed under 35 U.S.C. 371, unity of invention between different categories of inventions will only be found to exist if specific combinations of inventions are present. Those combinations include:

A) A product and a special process of manufacture of said product.

B) A product and a process of use of said product.

C) A product, a special process of manufacture of said product and a process of use of said product.

D) A process and an apparatus specially designed to carry out said process.

E) A product, a special process of manufacture of said product, and an apparatus specially designed to carry out said process.

The allowed combinations do not include multiple products, multiple methods of using said products, and a method of making a product as claimed in the instant application, see MPEP§ 1850).

In this case, the products are complement fusion protein versus polynucleotide. As is well known in the art, polynucleotides such as claimed by Applicant are transcribed into RNA and the DNA is translated into protein. Thus polynucleotides encode proteins. Complement fusion proteins are proteins that bind to other proteins. The two types of molecules therefore have different functions - the encoding of protein versus binding to other proteins, different modes of operation - transcription and translation versus protein-protein interactions - and different effects - production of protein versus interacting with another protein. Thus, they differ structurally and functionally and cannot be used together or interchangeably, reasons as to why the other groups are distinct are also provided in the previous office action. A product is distinct from a process of use if it has other uses. Methods are different if they have different method steps, goals, or outcome measures. Further, a prior art search also requires a literature search. It is a burden to search more than one invention.

Therefore, the restriction requirement is still deemed proper and is therefore made FINAL.

3. Claims 8-11 and 13 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-7, 12 and 14-18, drawn to a protein comprising: a first functional unit of a first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; a first spacer sequence of at least about 200 amino acids encoding a polypeptide that does not exhibit complement regulating properties, attached to the first functional unit; and a second functional unit attached to the spacer sequence, a polypeptide providing a functional unit of a second complement regulatory protein, a protein having at least 95 percent sequence homology to a protein having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ IDNO: 19 and SEQ ID NO: 23 and a method of regulating complement activity comprising administering an effective amount of said protein, are being acted upon in this Office Action.

5. Claim 7 is objected to because of the following informalities: Specifically, the punctuation mark "," is missing between CR1 CCPs at line 3; "Ig G4" should have been "IgG4".

6. The information disclosure statements (IDS) submitted on July 7, 2006 and November 3, 2006 have been fully considered and an initialed copy of the IDS is included with this Office Action.

7. Applicant should amend the first line of the specification to reflect the relationship between the instant application and provisional application 60/537,860 filed January 21, 2004 stated on the oath.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-7, 12 and 14-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a hybrid DAF-CR1B protein comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 13 as shown in Figure 13 and SEQ ID NO: 15 as shown in Figure 9A, (2) a hybrid DAF-Ig4 comprising the amino acid sequence of SEQ ID NO: 19, (3) a hybrid DAF-MCP polypeptide comprising the amino acid sequence of SEQ ID NO: 23, and (4) a method of inhibiting classical pathway C3 and C5 convertase mediated or hemolysis comprising administering an effective amount of a hybrid DAF-CR1B protein comprising the amino acid sequence of SEQ ID NO: 13 or SEQ ID NO: 15 for inhibiting classical and alternative C3 convertase, **does not** reasonably provide enablement for any protein as set forth in claims 1-7, 12 and 16-18 and a method of regulating any complement activity by administering an effective amount of any protein comprising any first functional unit of any first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; any first spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties, attached to the first functional unit; and any second functional unit attached to the spacer sequence, selected from the group consisting of polypeptides providing a functional unit of a second complement regulatory protein, polypeptides derived from an immunoglobulin, and polypeptides

that enhance binding of the protein to an animal cell to any mammal such as human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The claims encompass a genus of protein comprising any first functional unit of any first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; any first spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties, attached to the first functional unit; and any second functional unit attached to the spacer sequence, selected from the group consisting of polypeptides providing a functional unit of a second complement regulatory protein, polypeptides derived from an immunoglobulin, and polypeptides that enhance binding of the protein to an animal cell.

Enablement is not commensurate in scope with how to make and use such protein without guidance as to the structure, i.e. amino acid sequence of such.

The specification discloses just human DAF comprising the amino acid sequence of SEQ ID NO:1, human CR1 comprising the amino acid sequence of SEQ ID NO: 3, and human MCP comprising the amino acid sequence of SEQ ID NO: 5 (Figure 4A). The specification exemplifies a fusion protein DAF-CR1B comprising a human DAF fused to human CR1B protein wherein the DAF-CR1B comprising the amino acid sequence of SEQ ID NO: 13 and SEQ ID NO: 15, a hybrid DAF-Ig4 fusion protein comprising the amino acid sequence of SEQ ID NO: 19, and a hybrid DAF-MCP fusion protein comprising the amino acid sequence of SEQ ID NO: 23. The DAF hybrid proteins mentioned above inhibit classical and alternative C3 convertase in vitro.

At the time of filing, the specification does not teach any make and use any protein comprising any first functional unit of any complement regulatory protein fused to any spacer

sequences of 200 or more amino acids and any second functional unit such as any polypeptide providing any functional unit of any second complement regulatory protein, any polypeptide derived from any immunoglobulin or any polypeptides that enhance binding of the protein to any animal as the second or third functional unit because of the lack of guidance as to the structure, i.e., amino acid sequence of protein.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

With respect to "amino acids *encoding* a polypeptide" in claim 1, amino acids do not encode any polypeptide. Only polynucleotide encodes a protein.

With respect "polypeptides *derived* from immunoglobulin", other than the Fc fragment of IgG4, there is insufficient guidance as which amino acids within the full-length sequence of which immunoglobulin to be substituted, deleted, added or combination thereof such that the derivatives of immunoglobulin still maintains receptor binding and effector functions. The specification discloses just the Fc fragment of IgG4 fused to C terminus of second linker of DAF-IgG4 fusion protein. The specification is silent multiple polypeptides *derived* from IgG4 is fused to the second linker as now claimed.

In addition to the lack of specific guidance as to the structure of such protein, there is a lack of *in vivo* working example for the claimed method of regulating any complement activity in all mammals. The term "regulating" encompasses stimulating as well as inhibiting, which are mutually exclusive. There is a lack of guidance as to which first and second functional units exhibits increasing classical or alternative complement activity and which functional units exhibits inhibiting classical or alternative complement activity in any and all mammals.

A method of regulating complement activity for treating diseases in mammal such as human in the absence of working example is unpredictable. For examples, while soluble DAF fused to IgG chimeric protein was effective in vitro, it efficacy was marginal in vivo, particularly in other species.

Song et al (J Clin Investigation 111(12): 1875-1885, June 2003; PTO 892) teach complement regulator from one species may not work in another species. For example, human CD59 and soluble human DAF are poor inhibitors of rodent complement relative to their activity against human complement with the exception of human DAF activity against the rat alternative pathway of activation (see page 1882, right col., in particular). As such, it is unclear which unspecified soluble fusion protein comprising any complement regulatory protein is effective to regulate any complement activity in all mammals.

Even if the first functional unit is CCPs 2 to 4 of DAF, the term "comprising" is open ended (claims 3 and 6). It expands the first functional unit of DAF fragment to include additional amino acids at either or both ends. There is no guidance as to what amino acids to be added such that the protein still maintains secondary and tertiary structure and function. Likewise, the term "comprising" is open ended (claim 7). It expands the second spacer of CCPs 4-5 of CR1 to include additional amino acids at either or both ends. There is no guidance as to which amino acids to be added.

With respect to protein having "at least 95 percent sequence homology" to any sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 23, homology is not identity. Even assuming it is meant for 95% sequence identity, a 95% sequence identity to SEQ ID NO: 15 is equal to 72 amino acids difference (SEQ ID NO: 15 has 1446 amino acids in length). There is a lack of specific guidance as to which 72 amino acids within the full-length sequence of SEQ ID NO: 15 to be substituted, deleted, added or combination thereof such that the modified protein still maintains structure and function, in turn, effective to regulate, i.e., increase or decrease complement activity *in vivo*. The specification provided no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein as well as the coding sequence thereof which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

For example, Seffernick et al (J Bacteriol 183 (8): 2405-10, April 2001; PTO 892) teaches that two proteins with 98% amino acid sequence identity were found to catalyze different reactions, where one protein has melamine deaminase activity and the other protein has atrzine chlorohydrolase activity (see Fig.3, page 2408; DISCUSSION section on page 2409).

Chica et al. (Curr Opin Biotechnol 16(4):378-84, August 2005; PTO 892) teaches that the complexity of the structure/function relationship in enzymes has proven to be the factor limiting

the general application of rational enzyme modification and design, where rational enzyme modification and design requires in-depth understanding of structure/function relationships. The positions within a protein's amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining a protein having the same biological activity are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

Given the lack of complement regulatory protein from species other than human, the lack of guidance, direction or working examples, and the state of the art being that it is unpredictable what the equivalent protein, if any, from other species would be or what function it would have, it would require undue experimentation to make the claimed protein within the metes and bounds of the claims that would be reasonably expected to have the desired effect in mammals.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

10. Claims 1-7, 12 and 14-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any protein as set forth in claims 1-7, 12 and 16-18 and a method of regulating any complement activity by administering an effective amount of any protein comprising any first functional unit of any first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; any first spacer sequence of at least about 200 amino acids *encoding a polypeptide*

that does not exhibit complement regulating properties, attached to the first functional unit; and any second functional unit attached to the spacer sequence, selected from the group consisting of polypeptides providing a functional unit of a second complement regulatory protein, polypeptides derived from an immunoglobulin, and polypeptides that enhance binding of the protein to an animal cell to any mammal such as human.

Claim 1 encompasses any protein comprising any first functional unit of any first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; attached to any first spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties, attached to any second functional unit of a second complement regulatory protein such as any polypeptides derived from an immunoglobulin, or any polypeptides that enhance binding of the protein to an animal cell.

Claim 2 encompasses any protein comprising any first functional unit of any first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; attached to any first spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties, attached to any second functional unit of a second complement regulatory protein such as any polypeptides derived from an immunoglobulin, or any polypeptides that enhance binding of the protein to an animal cell, attached to a second spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties, and attached to a third functional unit such as any polypeptides derived from any immunoglobulin or any polypeptides that enhance binding of the protein to any animal cell.

Claim 3 encompasses any protein comprising any first functional unit *comprising* at least CCPs 2, 3, 4 and 4 of any DAF attached to a first spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties, attached to any second functional unit of a second complement regulatory protein such as any polypeptides *derived* from an immunoglobulin, and polypeptides that enhance binding of the protein to any animal cell of any mammal such as human.

Claim 4 encompasses any protein comprising any first functional unit of any first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; a first spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties such as CCPs 8-10 of any Complement receptor 1 (CR1), CCPs 15-17 of any CR1, CCPs 1-4 of Membrane Cofactor Protein (MCP), any

polypeptides derived from IgG4 or any lipid tail attached to said first functional unit; and any second functional unit attached to the spacer sequence, selected from the group consisting of any polypeptides providing a functional unit of any second complement regulatory protein, any polypeptides *derived* from an immunoglobulin, and any polypeptides that enhance binding of the protein to an animal cell.

Claim 5 encompasses any protein comprising any first functional unit of any first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; any first spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties, attached to said first functional unit; and any second functional unit attached to said spacer sequence, wherein the second functional unit is any second complement regulatory protein, any polypeptides derived from an immunoglobulin, and polypeptides that enhance binding of the protein to an animal cell to any mammal such as human wherein the spacers are any sequence contains substantially all of the amino acids of CCPs 4-7 of any CR1 or substantially all of the amino acids of CCPs 11-14 of any CR1.

Claim 6 encompasses any protein comprising CCPs 1-4 of any DAF as the first complement regulatory protein, any first spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties such as substantially all of the amino acids of CCPs 4-7 of any CR1, attached to the first functional unit; and any second functional unit attached to said spacer sequence, wherein the second functional unit is CCPs 8-10 of any CR1, any CCPs 1-4 of MCP, or any polypeptides derived from IgG4.

Claim 7 encompasses any protein comprising any first functional unit such as CCPs 1-4 of any DAF complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; any first spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties such as substantially all of the amino acids of CCPs 4-7 of any CR1, attached to the first functional unit; and any second functional unit attached to the spacer sequence, wherein the second functional unit is CCPs 8-10 of any CR1, any CCPs 1-4 of MCP, any polypeptides derived from IgG4 and a second spacer comprising substantially all of the amino acids of CCPs 4-5 of any CR1, and a third functional unit such as CCPs 8-10 of any CR1, CCPs 1-4 of any MCP, or any peptides derived from IgG4.

Claim 12 encompasses any protein having at least *95* percent sequence *homology* to a protein selected from the group consisting of any proteins having the sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: NO: 23.

Claims 14 and 15 encompass a method of regulating complement activity comprising administering an effective amount of comprising a first functional unit of any first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; attached to any first spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties, attached to any second functional unit of a second complement regulatory protein such as any polypeptides derived from an immunoglobulin, or any polypeptides that enhance binding of the protein to an animal cell to any mammal, any mammal such as a human.

Claim 16 encompasses any protein comprising any first functional unit of any first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; attached to any first spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties, attached to any second functional unit of any second complement regulatory protein such as any polypeptides derived from an immunoglobulin, or any polypeptides that enhance binding of the protein to an animal cell, attached to a second spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties, and attached to a third functional unit such as any polypeptides derived from any immunoglobulin or any polypeptides that enhance binding of the protein to any animal cell and wherein the spacers are selected from the group consisting of substantially all of the amino acids of CCPs 4-7 of any CR1, and substantially all of the amino acids of CCPs 11-14 of any CR1.

Claim 17 encompasses any protein comprising any first functional unit *comprising* at least at least CCPs 2, 3, 4 and 4 of any DAF attached to a first spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties, attached to any second functional unit of any second complement regulatory protein such as any polypeptides derived from an immunoglobulin, and polypeptides that enhance binding of the protein to an animal cell to any mammal such as human and wherein the spacers are selected from the group consisting of substantially all of the amino acids of CCPs 4-7 of any CR1, and substantially all of the amino acids of CCPs 11-14 of any CR1.

Claim 18 encompasses any protein comprising any first functional unit of any first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; a first spacer sequence of at least about 200 amino acids *encoding a polypeptide* that does not exhibit complement regulating properties such as CCPs 8-10 of any Complement receptor 1 (CR1), CCPs 15-17 of any CR1, CCPs 1-4 of Membrane Cofactor Protein (MCP), any polypeptides derived from IgG4 or any lipid tail attached to said first functional unit; and any second functional unit attached to the spacer sequence, selected from the group consisting of any polypeptides providing a functional unit of a second complement regulatory protein, any polypeptides derived from an immunoglobulin, and any polypeptides that enhance binding of the protein to an animal cell and wherein the spacers are selected from the group consisting of substantially all of the amino acids of CCPs 4-7 of any CR1, and substantially all of the amino acids of CCPs 11-14 of any CR1.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., complete or partial structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, method of making the claimed invention, level of skill and knowledge in the art and predictability in the art sufficient to show that applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factor to

be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

The specification discloses just human DAF comprising the amino acid sequence of SEQ ID NO:1, human CR1 comprising the amino acid sequence of SEQ ID NO: 3, and human MCP comprising the amino acid sequence of SEQ ID NO: 5 (Figure 4A). The specification exemplified fusion protein (DAF-CR1B comprising a human DAF fused to human CR1B protein wherein the DAF-CR1B comprising the amino acid sequence of SEQ ID NO: 13 and SEQ ID NO: 15, a hybrid DAF-Ig4 fusion protein comprising the amino acid sequence of SEQ ID NO: 19, and a hybrid DAF-MCP fusion protein comprising the amino acid sequence of SEQ ID NO: 23. The DAF hybrid proteins mentioned above inhibit classical and alternative C3 convertase in vitro.

At the time of filing, applicants are not possession of a genus of protein comprising any first functional unit of any complement regulatory protein fused to any spacer sequences of 200 or more amino acids and any second functional unit such as any polypeptide providing any functional unit of any second complement regulatory protein, any polypeptide derived from any immunoglobulin or any polypeptides that enhance binding of the protein to any animal as the second or third functional unit because of the lack of guidance as to the structure, i.e., amino acid sequence of protein.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). As such, the structure of the claimed protein is not adequately described.

With respect to "amino acids *encoding* a polypeptide" in claim 1, amino acids do not encode any polypeptide. Only polynucleotide encodes a protein.

With respect "polypeptides *derived* from immunoglobulin", other than the Fc fragment of IgG4, there is insufficient guidance as which amino acids within the full-length sequence of which immunoglobulin to be substituted, deleted, added or combination thereof such that the

derivatives of immunoglobulin still maintains receptor binding and effector functions. The specification discloses just the Fc fragment of IgG4 fused to C terminus of second linker of DAF-IgG4 fusion protein. The specification is silent multiple polypeptides derived from IgG4 is fused to the second linker as now claimed.

In addition to the lack of specific guidance as to the structure of such protein, there is a lack of disclosure as how to regulate any complement activity in all mammals. The term "regulating" encompasses stimulating as well as inhibiting, which are mutually exclusive. There is a lack of guidance as to which first and second functional units exhibits increasing classical or alternative complement activity and which functional units exhibits inhibiting classical or alternative complement activity in any and all mammals.

A method of regulating complement activity for treating various diseases in any and all mammal such as human in the absence of working example is unpredictable. For examples, while soluble DAF fused to IgG chimeric protein was effective in vitro, it efficacy was marginal in vivo, particularly in other mammals.

For example, Song et al (J Clin Investigation 111(12): 1875-1885, June 2003; PTO 892) teach complement regulator from one species may not work in another species. Human CD59 and soluble human DAF are poor inhibitors of rodent complement relative to their activity against human complement with the exception of human DAF activity against the rat alternative pathway of activation (see page 1882, right col., in particular). As such, it is unclear which unspecified soluble fusion protein comprising any complement regulatory protein is effective to regulate any complement activity in all mammals.

Even if the first functional unit is CCPs 2 to 4 of DAF, the term "comprising" is open ended (claims 3 and 6). It expands the first functional unit of DAF fragment to include additional amino acids at either or both ends. There is no disclosure as to which amino acids to be added such that the protein still maintains secondary and tertiary structure and function. Likewise, the term "comprising" is open ended (claim 7). It expands the second spacer of CCPs 4-5 of CR1 to include additional amino acids at either or both ends. There is no guidance as to which amino acids to be added.

With respect to protein having "at least 95 percent sequence *homology*" to any sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 23, homology is not identity. Even assuming it is meant for 95% sequence identity, a 95% sequence identity to SEQ ID NO: 15 is equal to 72 amino acids difference since SEQ ID NO: 15 has 1446 amino acids in

length. There is a lack of specific guidance as to which 72 amino acids within the full-length sequence of SEQ ID NO: 15 to be substituted, deleted, added or combination thereof such that the modified protein still maintains structure and function, in turn, effective to regulate, i.e., increase or decrease complement activity in vivo. For example, Seffernick et al (J Bacteriol 183 (8): 2405-10, April 2001; PTO 892) teaches that two proteins with 98% amino acid sequence identity were found to catalyze different reactions, where one protein has melamine deaminase activity and the other protein has atrzine chlorohydrolase activity (see Fig.3, page 2408; DISCUSSION section on page 2409).

Chica et al. (Curr Opin Biotechnol 16(4):378-84, August 2005; PTO 892) teaches that the complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational enzyme modification and design, where rational enzyme modification and design requires in-depth understanding of structure/function relationships. The positions within a protein's amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining a protein having the same biological activity are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

Because the specification did not describe a variety of complement regulatory protein from other species other than SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 19 capable of performing the claimed activity for the claimed method and the skilled artisan would not be able to identify any such protein based on the specification's function description, the specification did not provide an adequate written description of the claimed genus. Accordingly, one of skill in the art would conclude that applicant was not in procession of the claimed genus as a whole at the time of filing. Therefore, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims 1-7, 12 and 14-18.

With respect to complement-regulating properties, this is amount to no more than a "wish" or "plan" for obtaining the claimed protein, rather than a description of the protein itself. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel,* 25 USPQ2d 1601 at 1606 (CAFC 1993)and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

In this case, the specification fails to disclose a representative number of species of each claimed genus, which includes many members with widely differing structural, chemical, and biological functions. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Further, the specification does not adequate describe the positions within a protein's amino acid sequence, the corresponding coding sequence where modifications can be made with a reasonable expectation of success in obtaining a protein having the same biological activity.

In this case, the specification provides fusion protein comprising human CCPs 1-4 fused to various CCPs 8-10 of human CR1 or CCPs 15-17 of human CR1 and CCPs 1-4 of human MCP or IgG4. Therefore, only protein comprising the amino acid sequence of SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 23 meet the written description provision of 35 U.S.C. § 112, first paragraph.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Further, possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound or molecule itself is required. See Fiers v Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inv. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

12. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "...amino acids *encoding*..." in line 3 of claim 1 and line 2 of claim 2 is indefinite because *amino acids* do not encode any protein. Only polynucleotide encodes a protein or polypeptide. Appropriate correction is required.

The term "substantially" in claims 5, 6, 7, 16, 17 and 18 is indefinite because the metes and bounds of what would constitute a "substantially all" cannot be determined. Such is a relative term, and neither the specification nor the claims provide adequate guidance to the interpretation of such term.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 3, 4, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 95/08570 publication (published March 30, 1995; PTO 892).

Claim 1 is interpreted to be a protein comprising: a first functional unit of a first complement regulatory protein i.e., DAF or MCP, wherein the first functional unit exhibits complement-regulating properties; a first spacer sequence of at least about 200 amino acids that does not exhibit complement regulating properties, attached to the first functional unit; and a

second functional unit attached to the spacer sequence, selected from the group consisting of polypeptides providing a functional unit of a second complement regulatory protein such as MCP or DAF since spacer sequence of at least 200 amino acids does not encode any polypeptide.

The WO 95/08570 publication teaches a chimeric fusion protein DAF-MCP comprising a first functional unit of a first complement regulatory protein such as DAF comprising the short consensus repeats CCPs 2, 3 and 4 of DAF (see page 11, lines 28-35 through page 12, in particular) a first spacer sequence such as a linker attached to said DAF that does not exhibit complement regulatory properties (see page 30, in particular) and a second functional unit of a second complement regulatory protein such as CCPs 1-4 of membrane cofactor protein (MCP) attached to said spacer (see abstract, claims 1-8, in particular). The first polypeptide such as DAF comprises at least regions 2, 3, 4 of decay accelerating factor short consensus repeats (see claim 8, in particular) and regions 1, 2, 3, 4 of membrane cofactor protein short consensus repeats (see page 25, line 15-17, in particular). The reference linker can range from 0 to 1500 amino acids which encompasses the claimed term of 200 amino acids (see page 12, line 19-20, in particular). The WO 95/08570 publication further teaches a chimeric fusion protein comprising MCP fused to DAF (see abstract, in particular). The WO 95/08570 publication also teaches a method of regulating complement activity by administering an effective amount of the reference chimeric fusion protein to a mammal such as a patient for reducing inflammation characterized by excessive complement activation (see claims 18-19 of the reference, pain particular). Thus, the reference teachings anticipate the claimed invention.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1, 2 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/08570 publication (published March 30, 1995; PTO 892) in view of Harris et al (J Biol Chemistry 278(38): 36068-36076, September 2003; PTO 892) as evidenced by Smith et al (J Immunol 154: 2226-2236, 1995; PTO 892).

The teachings of the WO 95/08570 publication have been discussed supra.

The invention in claim 2 differs from the teachings of the reference only in that the protein comprising a first functional unit of any first complement regulatory protein, wherein the first functional unit exhibits complement-regulating properties; attached to any first spacer sequence of at least about 200 amino acids that does not exhibit complement regulating properties, attached to any second functional unit of a second complement regulatory protein such as any polypeptides derived from an immunoglobulin, or any polypeptides that enhance binding of the protein to an animal cell, attached to a second spacer sequence of at least about 200 amino acids that does not exhibit complement regulating properties, and attached to a third functional unit such as any polypeptides derived from any immunoglobulin.

The invention in claim 4 differs from the teachings of the reference only in that the second functional domain is polypeptide derived from IgG4 instead of CCPs 1-4 of MCP.

Harris et al teaches fusion protein comprising a first complement regulatory protein such as the amino-terminal 1-4 short consensus repeat (SCRs) from DAF or CD59 fused to human IgG4 Fc domains via a spacer such as 75 amino acids of IGD sequences or MMP cleavage site between DAF4-IgG4 (see page 36070, right col., page 36071, Fig 1(a), Table 1, Figure 2B, in particular). The hybrid molecule has long plasma half life (see abstract, page 36070, right col., in particular). Harris et al teach short spacing between DAF and the antibody IgG4 Fc resulted in steric hindrance but fusion protein comprising a long spacer sequence between DAF and the antibody hinge partially restored function while the function was totally restored by papain or MMPs or aggrecanase at the cleavage site (see abstract, page 36069, left col., in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the MCP in the fusion protein comprising CCPs 1-4 of DAF, a spacer peptide ranges from 0 to 1500 amino acids and MCP of the WO 95/08570 publication for

the Fc domains of human IgG4 as taught by the Harris et al to form a new fusion protein comprising CCPs 1-4 of DAF, a spacer peptide ranges from 0 to 1500 amino acids and Fc of IgG4. In this case, simple substitution of one known element for another would obtain predictable results.

In the alternative, it would have been obvious to one of ordinary skill in the art at the time the invention was made to fuse the fusion protein comprising CCPs 1-4 of DAF, a spacer peptide ranges from 0 to 1500 amino acids and MCP of the WO 95/08570 publication to the human IgG4 Fc via a long spacer sequence of Harris to form a fusion protein comprising CCPs 1-4 of DAF, a spacer from 0 to 1500 amino acids, MCP follows by a spacer from 0 to 1500 amino acids, and the Fc of IgG4. In this case, combining prior art elements according known methods would yield predictable results. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to substitute MCP for Fc of IgG4 because Harris et al teach IgG4 fusion protein comprising CCPs 1-4 of DAF increases plasma half life of the fusion protein (see abstract, page 36070, right col., in particular). Evidentiary reference Smith et al teach the Fc of IgG4 normally devoid of complement activity (see abstract, in particular).

One having ordinary skill in the art would have been motivated to increase the length of the spacer between first, second and third functional domains of complement regulatory protein because short spacer sequence caused steric hindrance and longer spacer sequence restore activity of the complement regulatory functional subunits as taught by Harris et al (see abstract, page 36069, left col., in particular). It is within of one of ordinary skill in the art to lengthen any spacer sequence to remove any steric hindrance.

18. SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 23 are free of the art.

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate

Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The IFW official Fax number is (571) 273-8300.

21. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644